

The Stanford Cardiovascular Institute provides a home for cardiovascular research across the Stanford campus. As a center of intellectual and scientific activity, the CVI provides resources to its members to stimulate discovery, translation, and implementation of new treatments, diagnostics, and preventative medicine. The mission of the CVI is to lift the burden of cardiovascular disease.



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2010 was a significant year for the Stanford Cardiovascular Institute. New initiatives and events fostered research that gained public notice and federal funding. Membership continued to grow, representing disciplines from across the University and Medical School. 2010 also saw the implementation of a strategic plan for the CVI—a document that benchmarks our operation against other institutes and provides a roadmap for future growth.

As the home for cardiovascular science at Stanford, the CVI funds cutting edge research and new collaborations through its seed grants. In 2010, five grants were awarded to address a fundamental question: How does the cardiovascular system age? Funded projects addressed the question from a variety of disciplines including genomics, metabolics, bioengineering, cell biology, and population science. The CVI seed grant program has been hugely successful—past research has attracted approximately \$50 million in large agency grants.

Regenerative medicine in cardiovascular science at Stanford took off in the last year, with significant publications and several million dollars in new grants. Of the nine Progenitor Cell Consortium research hubs funded by the National Heart, Lung and Blood Institute, three are at Stanford, all headed by CVI affiliates.

Also in 2010, the Vera Moulton Wall Center became part of the CVI, bringing with it fascinating and powerful research in pulmonary vascular disease. Stanford boasts internationally recognized experts in pulmonary hypertension, whose talents add to the wealth of collaborative and innovative opportunities within CVI.

Education and training of future leaders in cardiovascular research and treatment is a prime focus of the CVI. In 2010, the institute was awarded an NIH training grant that will fund up to six trainees each year in vascular biology and disease. Training grants in myocardial biology and cardiovascular imaging at Stanford provide a repertoire of cardiovascular training opportunities. In addition, private donor funds underwrote three fellowships supporting a graduate student in chemical engineering, and postdoctoral fellows in chemical & systems biology and in imaging. The past year saw the first symposium to address the basic and translational science of sex differences, a meeting organized by the CVI, which brought together researchers from all the Stanford Institutes of Medicine and from Women's Health at Stanford. More than 100 attendees spent the day discussing the role of sex chromosomes on development and disease.

2010 was not the founding year of the CVI's existence, but it was a foundational year—one in which we built a strong foundation for the future. In the coming years, I anticipate that the institute and its members will continue to create opportunities for success in all our activities in research, education and clinical care as well.



Robert C. Robbins, MD

Robert C. Robbins  
Director, Stanford Cardiovascular Institute



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Thelma and Henry Doelger Professor of Cardiac Surgery  
Professor and Chairman of Cardiothoracic Surgery



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Professor of Cardiovascular Medicine



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Deputy Director, CVI  
Dwight and Vera Dunlevie Professor in Pediatric Cardiology



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Deputy Director, CVI  
Assistant Professor of Cardiovascular Medicine



### **Philip Tsao, PhD**

Deputy Director, CVI  
Associate Professor of Cardiovascular Medicine



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Director, Cardiac Catheterization and  
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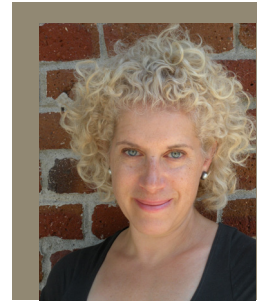
Martha Meier Weiland Professor of  
Medicine and Mechanical Engineering  
Co-Chair, Stanford University School  
of Medicine Bioengineering



**Sofie R. Kleppner, PhD**

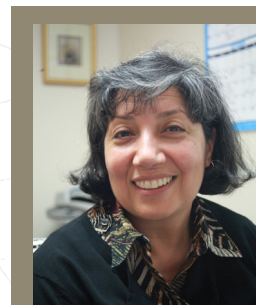
Associate Director

Sofie is responsible for implementing the strategic plan, for overseeing the research and education programs, and for developing new initiatives within the Institute. Sofie received a PhD in Neuroscience from the University of Pennsylvania, did her postdoctoral work at UCLA, and managed preclinical development for two small biotech companies before joining the CVI.

**Mitra Haddad**

Program Manager

Mitra joined the Stanford Cardiovascular Institute in June 2010. She is in charge of the day to day activities of the Institute. She came with over 15 yrs. of experience managing prominent regional sales and marketing offices of Scholastic and Pearson Foundation/Silver Burdett Ginn Educational Publishing companies as well as 6 years of experience at Stanford. Mitra's business degree is from Kingston University in Kingston, England where she was brought up.

**Phoebe Wall Howard**

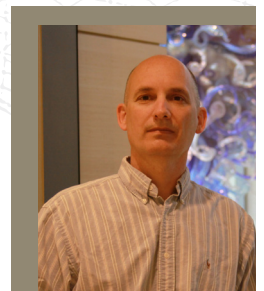
Associate Director, Development

Phoebe Wall Howard was hired as associate director of development for the Cardiovascular Institute in November. She came to Stanford from the San Francisco General Hospital Foundation, where her fundraising work focused on orthopaedic trauma. Howard has extensive background in political fundraising and media strategy. She is an award-winning journalist who reported on Arkansas Gov. Bill Clinton, the White House and California politics for Gannett Corp., McClatchy News Co., People magazine and CBS radio.

**Christopher Vaughan**

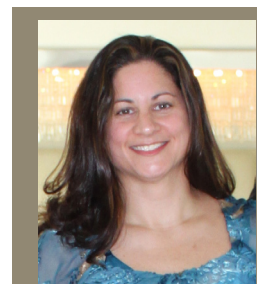
Communications Officer

Christopher Vaughan works on web, print and video communications strategies for the CVI, coordinating between the institute, the Medical School News and Information Office, and the Office of Medical Development. He is an author and has been an editor at Cambridge University Press, Science News Magazine, New Scientist Magazine, UC San Francisco and the National Institutes of Health. He earned a BS in biophysics from UC Berkeley.

**Danielle DeLeon**

Internet and Web Specialist

Danielle deLeon is the website administrator for the CVI and the Department of Cardiothoracic Surgery, which include the Divisions of Adult Cardiac Surgery, Thoracic Surgery, and Pediatric Cardiac Surgery. She came to Stanford School of Medicine in 2003 after earning her bachelors degree in computer science from the California State University, Monterey Bay.



Improvements in the cardiovascular health of patients arise from new research that translates scientific discoveries into practical clinical and public health applications. The institute provides organizational structure to concentrate and coordinate the activities of scientists, engineers, educators, and physicians committed to improving the cardiovascular health of patients and the general population.



John Cooke, MD, PhD and patient

The Cardiovascular Institute (CVI) is set in a fertile research environment comprising the School of Medicine, Stanford Hospital & Clinics, and Lucile Packard Children's Hospital, schools of Humanities and Sciences, Engineering, and Business. The institute and its university partners are geographically situated in Silicon Valley, an area with a strong culture of promoting and funding innovations in technology, science and medicine. This environment enables a richly diverse mix of students, faculty, and scientists to engage with each other in the institute's interdisciplinary research and training programs.



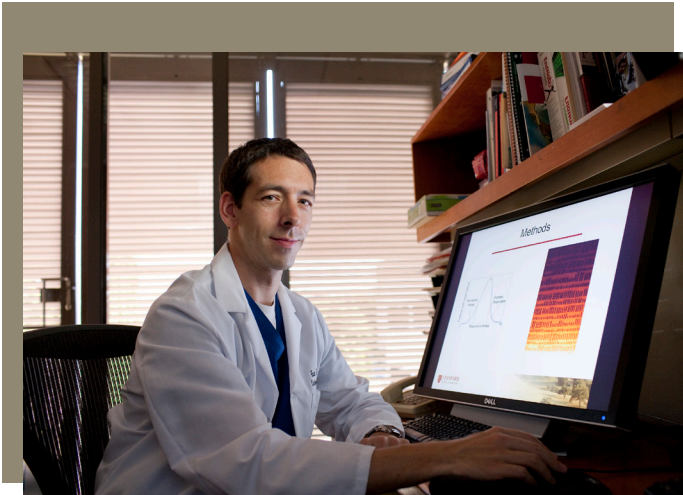
## Cardiomyopathies

Cardiomyopathies are diseases that limit the heart's ability to pump blood. This class of diseases, affecting 50,000 American adults and children, can cause the heart muscle to become thick (hypertrophic cardiomyopathy), to enlarge and stretch (dilated cardiomyopathy), or to become rigid (restrictive cardiomyopathy). All of these diseases can produce arrhythmias, heart failure or sudden death. Hypertrophic cardiomyopathy, though rare, is particularly insidious as it affects people of all ages, often tragically striking young people who are unaware that they have a problem.

### 2010 Highlight

#### **Physicians failing to follow recommended heart-failure treatment guidelines, study finds**

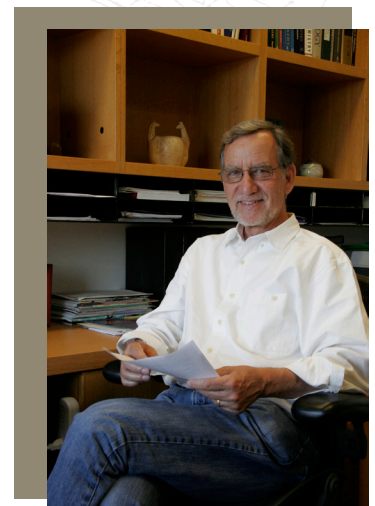
Physicians are losing ground in prescribing the types of medications that have proven most effective in treating a condition known as congestive heart failure, according to a study from CVI researchers. The study showed that the use of two types of drug therapy for treating heart failure has steadily declined since the early and mid-2000s, and that the medications are being prescribed to only about one-third of the patients who would benefit from them.



**Euan Ashley, MRCP, DPhil**

CVI scientists are expanding a major initiative to identify and treat the genetic determinants of hypertrophic cardiomyopathy (HC) through extensive screening of cardiomyopathy patients. Researchers have already found a number of genetic mutations associated with HC, and are now establishing complex models to understand the pathways through which these genes exert their effects. This work should lead to a deep understanding of the development and maintenance of the heart muscle and new drug targets. Children with congenital heart disease are susceptible to cardiomyopathy, and CVI researchers are identifying age-associated genes that may be manipulated to protect the hearts of this vulnerable population. In addition, researchers are using a multidisciplinary approach to explore the relationship between insulin resistance and idiopathic dilated cardiomyopathy, as well as the interaction of insulin, weight, and congenital heart disease.

In order to actively translate basic research into clinical advances, CVI researchers will build on the collaborations within the institute, using bioengineering, cell models, mouse models, large animal models and phase I clinical trials to test therapies for cardiomyopathy. In addition, researchers are leveraging existing cardiomyopathy registry data already at Stanford to conduct retrospective studies.



**James Spudich, PhD**

## Congenital Heart Disease

Congenital birth defects of the heart afflict about 35,000 newborns every year. In addition, there are about 500,000 adults in the US who were born with congenital cardiac birth defects. On the one hand, this statistic is encouraging because many of these people would have died in infancy without improvement in treatments, but they continue to live with the complications of their heart conditions. Stanford continues to build on its strong program in the treatment of congenital heart defects. Using new computational models for congenital heart disease, researchers can move discoveries into clinical practice more quickly and more accurately. Researchers continue to study cardiopulmonary development with an aim towards prevention, early diagnosis and improved treatments, including fetal therapy. Institute scientists can now integrate electrical, mechanical, cellular and genetic therapies to glean the molecular and physiological basis of heart failure. In order to improve surgical outcomes, the institute is pushing efforts in regenerative medicine, genomics, proteomics and bioengineering, and leading efforts to improve our understanding of organ rejection.



Daniel Bernstein, MD

### 2010 Highlight INTERMACS-Defined Morbidity and Mortality Associated With Pediatric Ventricular Assist Device Support at Stanford

The use of ventricular assist devices (VADs) to bridge pediatric patients to heart transplantation has increased dramatically over the last 15 years. In this report, CVI researchers presented the largest US single-center report of pediatric VAD use to date. They presented detailed descriptions of morbidity and mortality associated with VAD support, using standard Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS) criteria for pediatrics to facilitate the comparison of these results to other studies.

The researchers found that INTERMACS criteria can be successfully used to analyze pediatric VAD outcomes. These data serve as a baseline for future studies of VAD support in children and indicate good survival rates but considerable morbidity.



## 2010 Highlights Noteworthy Publications

### Functional coupling of valvular interstitial cells and collagen via $\alpha 2\beta 1$ integrins in the mitral leaflet

Stephens, E.H., Durst, C.A., Swanson, J.C., Grande-Allen, K.J., Ingels Jr., N.B., Miller, D.C., Cellular and Molecular Bioengineering.

### Use of a low-profile, compliant balloon for percutaneous aortic valvuloplasty

Yamen E, Daniels DV, Van H, Yeung AC, Fearon WF. Catheter Cardiovasc Interv.

### Transient stiffening of mitral valve leaflets in the beating heart

Krishnamurthy G, Itoh A, Swanson JC, Miller DC, Ingels NB. Am J Physiol Heart Circ Physiol.

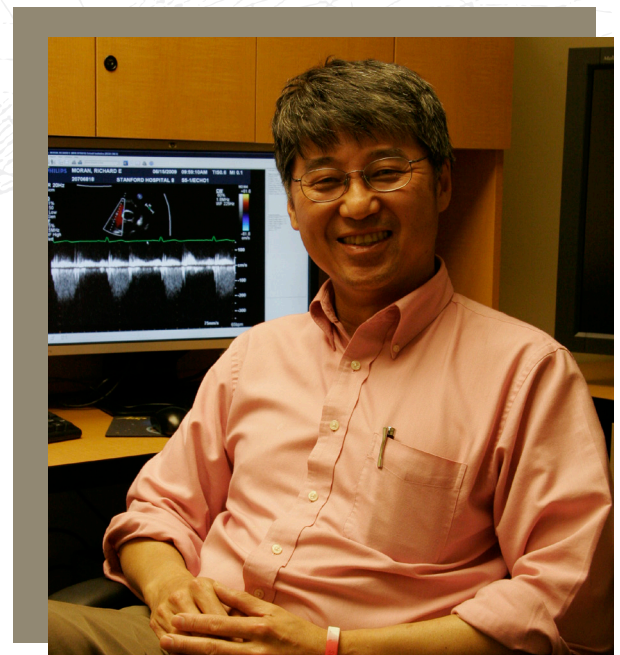
## Heart Valvular Disease

The valves of the heart are one of nature's most delicate yet hardy designs. When these few thin flaps of tissue fail to function properly, the efficiency of the heart is severely compromised. The institute plans to build on strong existing infrastructure to further elucidate the mechanisms of mitral regurgitation and the relationship of mitral regurgitation to left ventricular geometry and function. Building on strong collaborations between the mitral valve laboratory, cardiology, bioengineering and medical device companies, researchers are developing new methods for the surgical and percutaneous treatment of mitral valvular diseases.

The institute is advancing the diagnosis and repair of valvular disease by enhancing heart imaging capabilities, developing the program for percutaneous treatments, establishing a minimally invasive surgical program and incorporating age and sex-based differences into research.



Jennifer Tremmel, MD



David Liang, MD, PhD

## Heart Rhythm Disorders

Sixty to one hundred times a minute, every minute throughout a lifetime, the human heart engages in an exquisitely timed electro-mechanical dance – the heartbeat. Arrhythmias disrupt this dance and underlie a variety of ailments, from palpitations to sudden death. Stanford cardiovascular researchers have made significant contributions to the prevention, diagnosis and treatment of disorders that interfere with the rhythmic beating of the heart, yet there remains tremendous potential for further scientific and clinical advancements. Institute researchers are improving existing therapies and develop new ones in the areas of arrhythmia ablation and defibrillator and pacing systems. By understanding the genetic contributions to common arrhythmias, CVI researchers are creating novel anti-arrhythmia drugs and drug delivery systems. The vast array of new treatments focus on minimally invasive and non-invasive strategies to treat atrial fibrillation and ventricular tachycardia, and to improve implantable devices to treat ventricular arrhythmias. New avenues of exploration include the electrophysiological effects of stem cell therapies, novel imaging techniques to observe the heart's electrical activity in vivo, and clinical studies of novel therapies. Additionally, the institute is pursuing the overall goal of

### 2010 Highlight

#### **Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in atrial fibrillation**

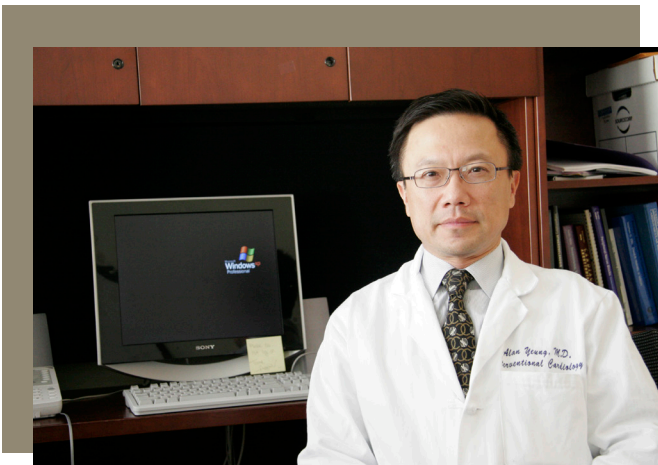
A newly approved drug may be a cost-effective way to prevent stroke in patients with an irregular heart rhythm — and may also offer patients better health outcomes than the commonly prescribed, but potentially risky, blood thinner warfarin, according to Stanford researchers. Dabigatran is the first new drug in 20 years to be approved for stroke prevention in atrial fibrillation. Electrophysiologist Mintu Turakhia, MD, MAS, and his colleagues found that for the average patient — 65 years and older with a risk of stroke — this drug has the potential to be a cost-effective alternative to warfarin, depending on how it is priced.

improving the practice of cardiac arrhythmia care through the use comparative effectiveness and outcomes research.



Paul Wang, MD





Alan Yueng, MD

## 2010 Highlight

### Stanford-led study disproves link between genetic variant, risk of coronary artery disease

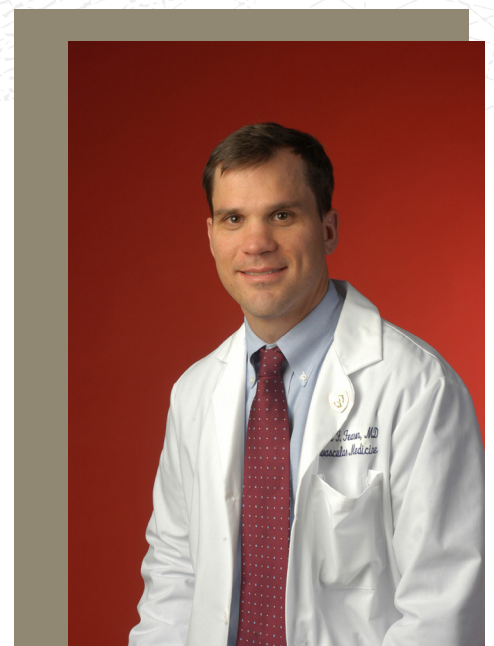
A genetic marker touted as a predictor of coronary artery disease is no such thing, according to a study led by CVI researchers. The study analyzed the data from more than 17,000 patients with cardiovascular disease and 40,000 others to assess whether carrying a particular variant of the KIF6 gene indicated a greater risk for coronary artery disease — a disease characterized by a buildup of cholesterol plaque in the walls of the arteries of the heart. The study found essentially no association between the gene variant and the risk of coronary disease.

## Coronary Artery Disease

Coronary artery disease (CAD), the narrowing or blocking of the arteries supplying blood to the heart muscle, is the most common cause of death in men and women over 20 years of age. While many Americans are aware of their risk of atherosclerosis, the underlying cause of CAD, severe disease may go unnoticed before a heart attack strikes. Sudden death may be the first indication of severe disease. Treatments and understanding of CAD have improved, but the disease remains a mystery in significant ways. The institute is supporting genomic, proteomic and imaging techniques, combined with better age and sex data, to better predict who will develop atherosclerosis, and to discover new drug targets. CVI researchers are developing and testing new pharmacological and invasive approaches to achieve prevention or regression of atherosclerosis. And researchers will develop and test new drugs and devices for treating atherosclerosis, as well as work to develop stem cell therapy for patients who cannot regain vascular function in other ways.



Thomas Quertermous, MD



William Fearon, MD

## Pulmonary Vascular Diseases

Stanford is particularly well situated to make progress in pulmonary hypertension and congenital vascular disease. Significant resources such as the Vera Moulton Wall Center are the foundation for significant advances in our basic understanding of these conditions and for finding new clinical treatments.

CVI researchers study the fundamental mechanics of cell walls and vessels to understand how their action is differentiated by sex, and how abnormal pathways lead to these diseases in either sex.



Jeffrey Feinstein, MD, MPH

Investigators will also focus on the immunological factors that lead to pulmonary hypertension, such as immune response to environmental factors, infectious disease and abnormal gene regulation. CVI researchers are improving the imaging of small vessels and lungs, identifying the risk factors leading to arterial hypertension with particular attention on age and sex differences. They also continue to develop new modeling tools for planning patient-specific treatment of congenital vascular disease.



Marlene Rabinovitch, MD

### The Vera Moulton Wall Center

This year the Vera Moulton Wall Center became a part of the CVI. The Wall Center seeks to enhance the lives of patients with pulmonary vascular disease by providing the highest level of clinical care, providing advanced training opportunities for physicians and other health care providers, and participating in clinical and bench-top research in pulmonary vascular disease.

Lucile Packard Children's Hospital/Stanford University Hospital is one of the few centers in the United States currently offering diagnostic and advanced therapeutic services to both adults and children with pulmonary hypertension.

### 2010 Highlight

**Prolonged mechanical ventilation with air induces apoptosis and causes failure of alveolar septation and angiogenesis in lungs of newborn mice.**

Defective lung septation and angiogenesis, quintessential features of neonatal chronic lung disease (CLD), typically result from lengthy exposure of developing lungs to mechanical ventilation (MV) and hyperoxia. This study is the first to show that prolonged MV of developing lungs, without associated hyperoxia, can inhibit alveolar septation and angiogenesis and increase apoptosis and lung elastin, findings that could reflect stretch-induced changes in VEGF and TGFbeta signaling, as reported in CLD.

## Aortic Disease

Complex, rare, and hard to diagnose, aortic disease kills over 50,000 people annually in the United States. Abdominal aortic aneurysm (AAA) disease alone is the 13th leading cause of death in adults, and the third leading cause of sudden death in men over age 65. Aortic dissections, thoracic and thoracoabdominal aortic aneurysms, and syndromic aortic disease such as Marfan's syndrome are responsible for thousands of additional aortic disease deaths each year. Advances in the care of patients with these challenging diseases will require improved methods of identifying patients at risk, tracking disease progression when recognized, and expanding treatment options beyond the high-risk surgical solutions available today.

Investigators within the CVI are using world-class tools to investigate the complex pathophysiology of aortic diseases, including the underlying genetic and biochemical processes that promote aortic aneurysmal degeneration in men and women. Work continues on translating molecular imaging modalities into effective monitoring strategies to optimize treatment for individual patients. Stanford faculty already have accumulated the largest cohort of early abdominal aortic disease patients in the world today, and are employing high-speed gene sequencing methods to identify individuals at risk, and using molecular biology to understand the mechanisms that cause aortic disease once the relevant genes are identified. New knowledge developed from these investigations improve current medical devices and surgical techniques to treat advanced disease and is driving the development of novel medical therapies to delay or ultimately prevent the need for surgical intervention.

Stanford is recognized world-wide for innovation and expertise in the evaluation and management of aortic diseases. Leading edge research currently ongoing within the CVI is positioning Stanford to lead an entirely new revolution in disease recognition and management.



**Ronald Dalman, MD**

### 2010 Highlight

#### **New treatment for severe aortic stenosis shown to save lives, researchers say**

Implantation of a new bioprosthetic-tissue valve into the hearts of patients who have severe aortic stenosis and are too sick or too old for open-heart surgery has been found to both save lives and improve the quality of those lives, according to a new multicenter study. Stanford was one of 21 institutions to participate in the study, known as the PARTNER Trial, which was the first comparing the efficacy of a transcatheter heart valve with routine medical therapy.



## Venous Disease

CVI hosts a multidisciplinary, translational research program for the investigation of novel mechanisms to diagnose and treat deep venous thrombosis. Venous disease is a broad category of disorders that may also involve immune activity as a common causative pathway. In all research on the incidence, treatment, and outcomes of venous disease, investigators include considerations of age- and sex-based differences as a primary element of their research.

## Peripheral Artery Disease

Peripheral artery disease (PAD), the obstruction of arteries in the arms and legs, affects up to a quarter of those over 55 years of age, though most people are asymptomatic. A serious disease itself, PAD is also a strong predictor of coronary artery disease and cerebrovascular disease. Hypertension, smoking, diabete, inflammation and high cholesterol are associated with the underlying disease.

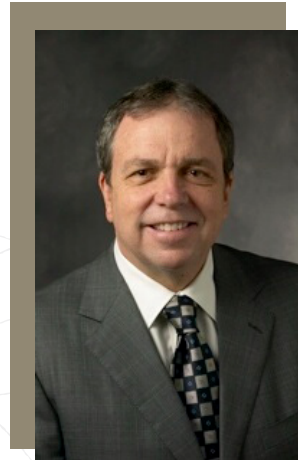
The Cardiovascular Institute program in PAD is focused on building new blood vessels, reversing vascular aging and restoring vascular health in men and women. This program emphasizes the discovery of the age, sex, genetic, and environmentally related determinants of peripheral artery disease using molecular investigation, genome-wide arrays and population studies, and the discovery of new biomarkers for disease and regeneration.

### 2010 Highlight

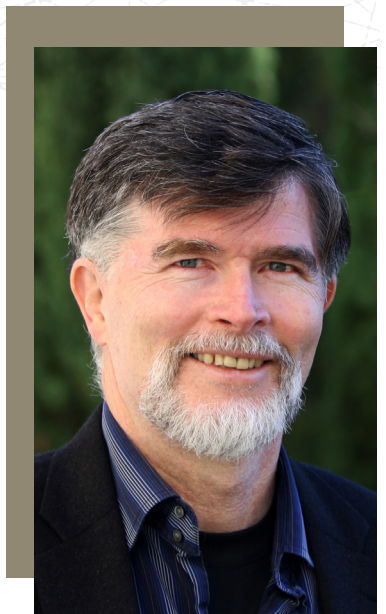
#### **Asymmetric dimethylarginine correlates with measures of disease severity, cardiovascular events and mortality in PAD**

Peripheral arterial disease (PAD) is associated with major cardiovascular morbidity and mortality. Abnormalities in nitric oxide metabolism due to excess of the NO synthase inhibitor asymmetric dimethylarginine (ADMA) may be pathogenic in PAD. Researchers in the Cooke lab explored the association between ADMA levels and markers of atherosclerosis, function, and prognosis. ADMA was a significant predictor of a major adverse cardiovascular event (MACE), independent of other risk factors including age, sex, blood pressure, smoking history, diabetes and ABI. Agents that target this pathway may be useful for this patient population.

Furthermore, institute researchers are developing novel therapies to treat PAD through the identification of drug targets, development of therapeutic agents, pre-clinical studies, first in-human trials, clinical trials and community intervention studies. Novel imaging methods and new nanodevices to monitor and modify vascular structures will ultimately lead to new treatments and



**Michael Dake, MD**



**John Cooke, MD, PhD**

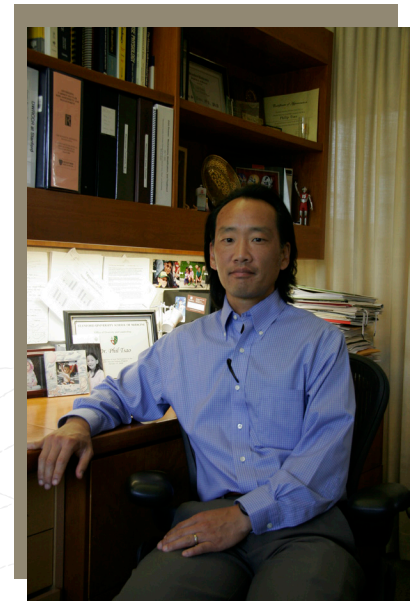
## Genomics, Proteomics and Bioinformatics

Stanford stands at the forefront of technology to unravel the personal genome. CVI researchers now lead the field in determining how to use information contained in the arrays of genes and proteins expressed in health and in disease, in young and in aged patients. By understanding the complex interplay of genes and proteins, researchers will gain the power to predict disease risk, to improve diagnosis, and to create new and better therapies. The CVI is expanding its existing DNA cohorts in coronary artery disease, insulin resistance and hypertension, peripheral artery disease and abdominal aortic aneurysm (AAA). It will expand sex- and age-based DNA cohorts



**Stephen Quake, MD and Euan Ashley, MRCP**

genetic variations most relevant to cardiovascular disorders. The expertise in statistics, genetics, and molecular biology enables resolution of complex networks of genes, allowing the fine detail of biological systems to be mined for new drug targets and therapeutic interventions.



**Phil Tsao, PhD**

in studies of heart failure, transplant, arrhythmia, idiopathic cardiomyopathy, pulmonary hypertension and congenital heart disease, so that the susceptibility to disease, and response to treatment, can be accurately assessed.

Stanford is in a unique position to capitalize on powerful genetics, bioengineering, and bioinformatics expertise on campus to develop high-throughput sequencing that can detect uncommon

### 2010 Highlight

**Study first to analyze individual's genome for risk of dozens of diseases, potential responses to treatment**

For the first time, researchers used a healthy person's complete genome sequence to predict his risk for dozens of diseases and how he will respond to several common medications. The risk analysis, from the Stanford University School of Medicine, also incorporated more traditional information such as a patient's age and gender and other clinical measurements.

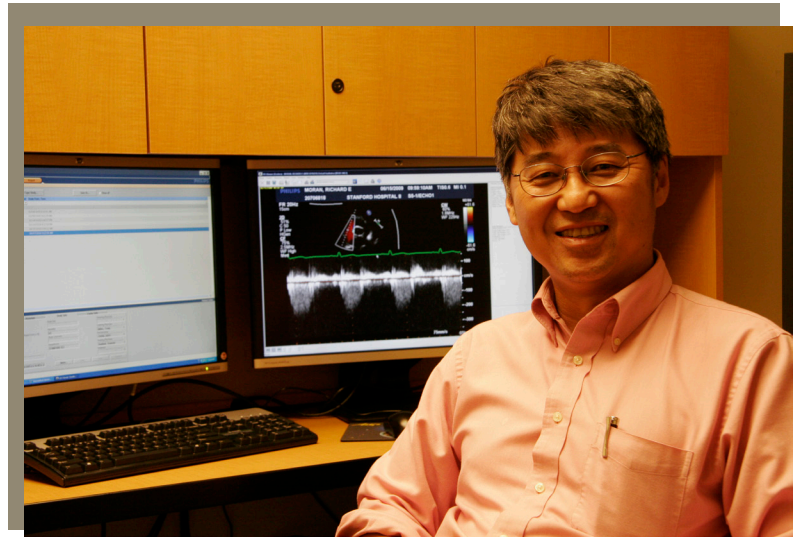


**Tom Quertermous, MD**



## Imaging

Stanford is the birthplace and developing ground for imaging technologies and techniques that have transformed the field. The CVI has a solid foundation for developments that will have a large impact on cardiovascular research and clinical care. New MRI techniques provide detailed assessment of cardiovascular disease noninvasively, from characterizing complex 4D blood flow in patients to precise tissue characterization of cardiomyopathy and stem cell delivery to targeted cellular and molecular contrast agents for early detection of atherosclerosis.



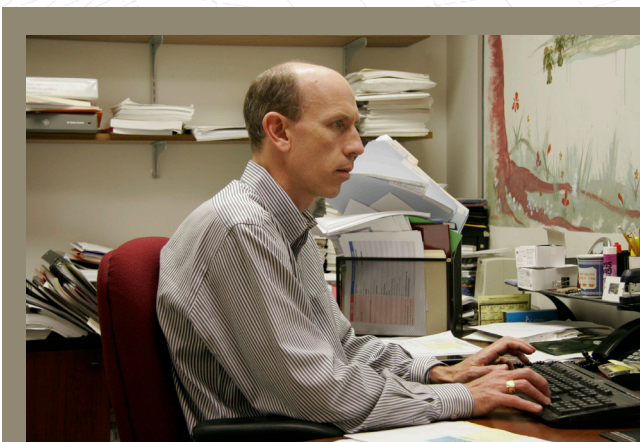
David Liang, MD, PhD

New CT approaches are now being developed to provide higher spatial and temporal resolution of coronary arteries with less radiation, while also more precisely quantifying stenosis severity and overall plaque burden. Further refinements may enable combined measurement of CT myocardial perfusion – a sensitive measure of disease and treatment success. 3D echo and ultrasound technology are now routine, providing pre-operative and intra-operative guidance of new complex interventional procedures, such as catheter-based valve replacement. Ultrasound can also be focused as a form of non-invasive therapy, enhanced by real-time MRI guidance. Additionally, rapid advances in PET and molecular imaging provide a noninvasive “window” into the complex biology that goes on inside the heart and blood vessel wall, leading to better diagnosis, prediction, and basic scientific understanding of health and disease.

### 2010 Highlight

#### Human ferritin cages for imaging vascular macrophages

Atherosclerosis is a leading cause of death worldwide. Macrophages are key components of vascular inflammation, which contributes to the development and complications of atherosclerosis. Ferritin, an iron storage and transport protein, has been found to accumulate in macrophages in human atherosclerotic plaques. The authors hypothesized that ferritin could serve as an intrinsic nano-platform to target delivery of imaging agents to vascular macrophages to detect high-risk atherosclerotic plaques. They showed that engineered human ferritin protein cages are taken up in vivo by macrophages in murine atherosclerotic carotid arteries and can be imaged by fluorescence and magnetic resonance imaging. These results indicate that human ferritin can serve as a nanoparticle platform to image vascular inflammation in vivo.



Michael McConnell, MD

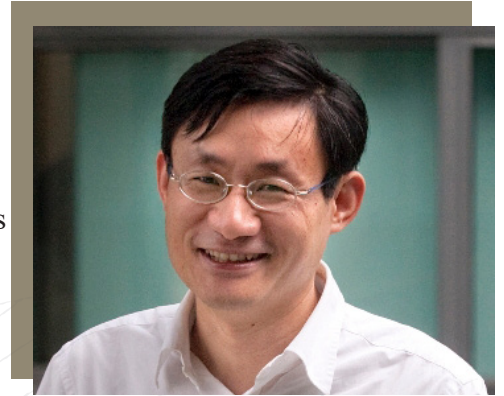
## Cellular and Molecular Biology

The institute has a rich history of supporting dialog between basic scientists and clinical researchers to identify opportunities for translating cellular and molecular findings into clinically relevant therapies for cardiovascular disease in women and men across the lifespan. Examples of ongoing

research that may have clinical applications include analysis of changes in: signal transduction central to the mechanics of heart disease; protein activation affecting the endothelial lining of blood vessels; gene patterns in *c. elegans* relevant to cardiovascular disease; cell signaling events driving cardiac cell development.



P.J. Utz, MD



Ching-Pin Chang, MD, PhD

### 2010 Highlight Upregulation of the apelin–APJ pathway promotes neointima formation in the carotid ligation model in mouse

To investigate apelin–APJ (angiotensin receptor-like 1) signalling in vascular remodelling, CVI researchers examined the pathophysiological response to carotid ligation in apelin knockout mice. The data suggest that increased apelin receptor expression by smooth muscle cell provides a paracrine pathway in injured vessels that allows endothelial-derived apelin to stimulate their division and migration into the neointima.

### 2010 Highlight Chromatin regulation by Brg1 underlies heart muscle development and disease

Cardiac hypertrophy and failure are characterized by transcriptional reprogramming of gene expression. Cardiac stress triggers adult hearts to undergo hypertrophy and a shift from  $\alpha$ -myosin heavy chain to fetal  $\beta$ -MHC expression. Ching-Pin Chang and colleagues showed that Brg1, a chromatin-remodelling protein, has a critical role in regulating cardiac growth, differentiation and gene expression. BRG1 is activated in certain patients with hypertrophic cardiomyopathy, its level correlating with disease severity and MHC changes. These studies show that Brg1 maintains cardiomyocytes in an embryonic state, and demonstrate an epigenetic mechanism by which three classes of chromatin-modifying factors—Brg1, HDAC and PARP—cooperate to control developmental and pathological gene expression.

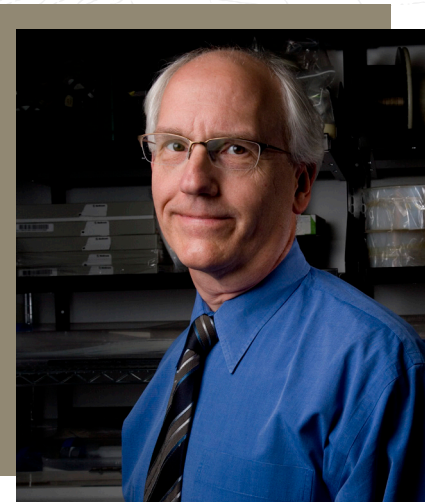


## Bioengineering

Stanford is a leader in bioengineering innovation, producing new patents and new treatments in every area of medicine. The cardiovascular system, with its heart as pump and its vessels as plumbing, is a natural focus of bioengineering research. Continuing bioengineering efforts implement multiscale, predictive modeling to understand cardiovascular disease at all levels, from the genome to the whole body. Collaborations between bioengineers and molecular biologists are leading to successful efforts to engineer and model cardiovascular cell and tissue development. These engineered tissues, cultured cardiomyocytes or even whole tissues grown in the laboratory may be central to future treatments. New imaging technologies and techniques for visualizing cardiovascular tissues and function, together with new devices and materials for treating cardiovascular disease, will provide better treatments and better diagnostics.



Beth Pruitt, PhD



Paul Yock, MD

### 2010 Highlight

#### **Matrix density mediates polarization and lumen formation of endothelial sprouts in VEGF gradients**

Endothelial cell (EC) sprouting morphogenesis is a critical step during angiogenesis, the formation of new blood vessels from existing conduits. Sarah Heilshorn studied three-dimensional sprouting morphogenesis using in vitro microfluidic devices that enabled the separate and simultaneous tuning of biomechanical and soluble biochemical stimuli. Quantitative analysis of endothelial sprout formation demonstrated that the ability of vascular endothelial growth factor (VEGF) to regulate stable sprout formation was mediated by the density of the surrounding collagen/fibronectin matrix. The author's results demonstrated that matrix density mediates VEGF-induced sprout polarization and lumen formation, potentially by regulating the balance between EC migration rate and proliferation rate.

## Population Science

Beyond basic, clinical, and translational science, population science addresses the health of entire groups. Sophisticated methods allow CVI researchers to study when and how cardiovascular interventions are best implemented. CVI population scientists are leaders in comparative effectiveness research, a topic that is central to national health policy. In collaboration with major health providers such as Kaiser Health System, the Stanford Cardiovascular Outcomes Research Center is examining large groups of patients and gleaning critical information about the epidemiological underpinnings of cardiovascular disease and treatment.



Mark Hlatky, MD

### 2010 Highlight

#### **Report contradicts FDA warning against use of anti-clotting drug with proton-pump inhibitors**

It's appropriate for heart patients who need to take the anti-clotting drug clopidogrel (brand name Plavix) and who also have a high risk of gastrointestinal bleeding to receive a prescription for acid-reducing medications called proton-pump inhibitors—such as pantoprazole (brand name Protonix)—according to a consensus document issued by three medical groups. The benefits outweigh the potential risks, according to the document, which contradicts last year's warning to patients by the U.S. Food and Drug Administration that the two therapies should not be combined because the proton-pump inhibitors could reduce the efficacy of clopidogrel by 50 percent.

### 2010 Highlight

#### **ECG testing of young athletes cost-effective in preventing deaths, study shows**

Routine testing of the hearts of young American athletes using electrocardiograms to screen for sudden death is “reasonable in cost and effective at saving lives,” according to a study by CVI cardiologists. The findings challenged the conventional wisdom in the United States that conducting routine electrocardiograms is too expensive to be required of young American athletes prior to engaging in competitive exercise, despite saving lives. The study was published in the March 2 issue of the *Annals of Internal Medicine*.



## Age and Sex Differences

Over two decades of research shows that sex and age influence all aspects of cardiovascular disease—its incidence and frequency, symptoms and signs, disease course, and treatment outcome. Unfortunately, research on sex and age differences remains sparse and fragmented.



Jennifer Tremmel, MD and Marcia Stefanick, PhD

The Cardiovascular Institute at Stanford is in a unique position to conduct the cross-disciplinary research necessary to understand these differences, and to implement recommendations based on this research throughout the medical community. Stanford already has a number of research concentrations - such as coronary pathophysiology, peripheral arterial disease, and electrophysiology- in which sex and age differences play an integral role. The task is to delve into other cardiovascular areas, and to help those outside of Stanford incorporate sex and age differences into their research and clinical practice.

The CVI is enlisting all areas of cardiovascular research to consider sex and age when conducting studies in genetics, proteomics, cellular biology, animal research, drug development and testing, device design and development, and clinical trials. Simple tools and considerations will dramatically improve our understanding through optimal experimental design and data capture. New statistical tools to assess optimal epidemiological and statistical methods for conducting sex and age differences research will underlie quick translation of research into clinical practice.

### 2010 Highlight Symposium on effects of sex chromosomes

Sex differences shape medical outcomes, and they may shape cures, too. That theme resonated throughout a June 11, 2010 CVI-sponsored research symposium discussing the biological and environmental causes and medical consequences of sex differences. About 100 people attended the all-day event, titled “Beyond X and Y: The basic and translational science of sex differences,” co-hosted by Women’s Health at Stanford and the Stanford Cardiovascular Institute and held in the Arrillaga Alumni Center.

## Program in Regenerative Medicine

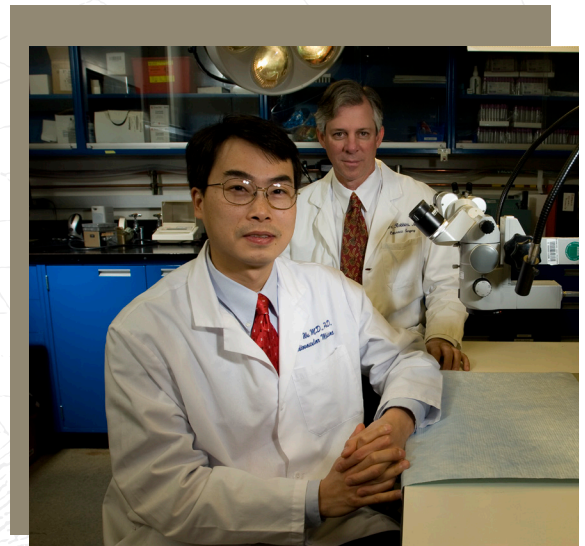
Studies in regenerative medicine at Stanford reflect the power of the CVI in supporting and directing critical interdisciplinary research in regenerative medicine. CVI-funded seed grants for projects too new and innovative to procure funding from federal sources supported several projects aimed at developing new cell sources, and new methods for guiding cellular development to treat cardiovascular disease. Based on subsequent publications and grant awards, these funds were well spent. The CVI now brings together top researchers in each of the crosscutting disciplines to address a single issue: Can we repair cardiovascular structure and function, and

restore health, using cell-based therapy? Three groups, each headed by CVI members, received prestigious NHLBI Progenitor Cell awards. The NHLBI funded a total of 9 projects, with \$170 million. The CVI scientists include experts in cellular and molecular science, imaging, bioengineering, population science, and genomics.

### 2010 Highlight

#### **Virus-free technique enables scientists to easily make stem cells pluripotent, moving closer to possible human therapies**

CVI scientists found that minicircles of DNA were the key to a new and easier way to transform stem cells from human fat into induced pluripotent stem cells for use in regenerative medicine. Unlike other commonly used techniques, the method, which is based on standard molecular biology practices, does not use viruses to introduce genes into the cells or permanently alter a cell's genome.

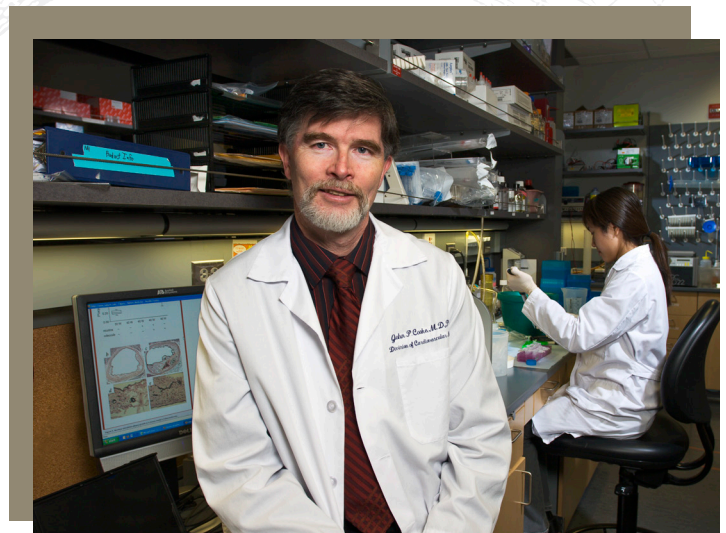


**Joseph Wu, MD, PhD and Robert Robbins, MD**

### 2010 Highlight

#### **Endothelial cells derived from embryonic stem cells repair tissue damaged by ischemia**

Dr. Ngan Huang and colleagues in the laboratory of John Cooke showed that endothelial cells derived from mouse embryonic stem cells (ESCs) could incorporate into the vasculature of a hind limb damaged by ischemia, increasing capillary density and improving blood flow. When these cells were injected intravenously, they were able to find their way to the damaged limb, take up residence and begin functioning.



**John Cooke, MD, PhD**



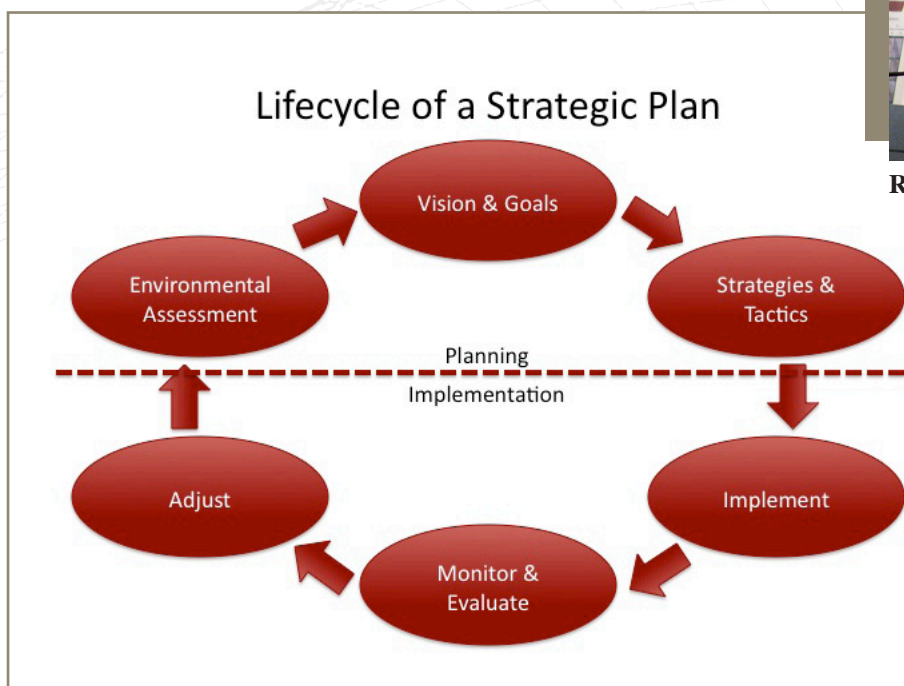
## Implementing the Strategic Plan

The CVI strategic plan is a living document. Replete with implementation strategies and with milestones of success, the plan provides a structure for tracking how quickly the Institute reaches its goals, and for developing new ones. Measures include: faculty recruitment; Institute space; education & training programs; tracking of CVI member publications and grant awards; progress reports from its fellows and seed grant recipients; new intellectual property generated; fellowships and seed grants; Institute space; core facilities; fundraising, including gifts and endowments; training grants; community outreach; invited speakers; symposia.

The CVI has already achieved some of its milestones and the future looks bright. A physical home in the new Stanford Medical Center will house CVI faculty. A new training grant in vascular disease will support six postdoctoral fellows annually. CVI member publications topped 300 in 2009. Seed grants led to several million dollars in federal funding. A new endowed fund will support two students annually. A new symposium on sex differences attracted nationally recognized speakers and an audience that spanned the Stanford research community. Three major, multi-million dollar awards from the NHLBI to CVI members will fund studies of regenerative medicine in cardiovascular and pulmonary disease.



Robert C. Robbins, MD



One of the institute's prime missions is to promote education about cardiovascular disease and cardiovascular medicine, not only in the academic community, but also amongst the public.

A meaningful cardiovascular education engages people at all educational levels at Stanford and provides a full spectrum of experiences. This includes not only continuing to develop a first-rate education for medical students, but also providing cardiovascular educational opportunities for graduate students in other disciplines such as engineering, and to expose undergraduates to cardiovascular science and bioengineering.

In the last year, the institute provided a number of forums for students, post-docs and faculty to exchange research ideas. These include:



Poster session at the annual CVI retreat, Sept. 2010

- **Lecture Series: Frontiers in Cardiovascular Science.** This weekly lecture series brings in a forum for cutting-edge research presented by Stanford scientists and visiting lecturers.
- **Fridays at Falk:** This weekly series features current research from post-docs and graduate students, providing a forum to exchange ideas and to sharpen presentation skills. The Friday afternoon seminar is also a chance for faculty and students to socialize a little at the end of the week.

## 2010 Highlight Promoting Science Education

In a JAMA article, CVI researchers surveyed the worsening state of science education and advocated for university intervention in precollege science education. The researcher looked at the results of the Stanford Medical Youth Science Program, a 5-week summer residential program for low-income, predominately black, Latino, and Native American high school students. Based on the statistics from the over 500 students who have passed through the Stanford program, active participation of universities in precollege science education can complement traditional approaches to learning science in classroom settings, help elevate science education as a national priority, and create an expanded pipeline for an educated workforce in scientific and health professions.

- **MED 223 Cardiovascular and Pulmonary Sciences Seminar:** The purpose of this course is to familiarize medical students with the spectrum of basic, clinical and translational CVI research beyond their specific area of chosen investigation.
- **CVI Retreat:** The annual CVI retreat gives researchers, post-docs and graduate students the opportunity to hear details of the full breadth of research going on at the institute. A distinguished guest speaker from another research university also provides valuable perspectives from cardiovascular research outside Stanford.
- **CVI Fellowship Training Program:** The Cardiovascular Institute funds a total of 6 postdoctoral fellows for two years each through the National Institutes of Health T32 training grant "Mechanisms & Innovation in Vascular Disease" co-directed by Drs. Ronald Dalman and John Cooke in 2010-2015.



## 2010 CVI Seed Grants

**Five \$50,000 seed grants were awarded in 2010 addressing the question: How does the cardiovascular system age?**

**Comprehensive and real time assessment of a genetic risk score for cardiovascular disease in the Women's Health Initiative.** PI: T. Assimes. Collaborators: John Ioannidis, Marcia Stefanick, Manisha Desai, Josh Knowles and Marco Perez.

Recent advances in genetics have facilitated the identification of susceptibility loci for coronary atherosclerosis and its risk factors. Here, we propose to use the rich bio-resource formed by the Women's Health Initiative to develop an infrastructure that will comprehensively and in real time assess the utility of a multi-locus genetic risk score (GRS) for CAD in women  $\geq 50$  years of age. Importantly, the make-up of this bio-resource will provide us with enough power to test the modifying effect of age on GRS. The results of this study will provide the scientific community with valuable insights into the pathophysiology of early vs. late onset atherosclerosis disease in women as well as differences in the pathophysiology between men and women. The results will also allow the scientific community to gauge the appropriate time to conduct key large-scale clinical trials to prove the utility of GRS in women.

**Effects of Aging and Gender on Abdominal Aortic Aneurysm Development, and the Role of MicroRNAs.** PI: J. Spin. Collaborators: Junya Azuma, Alicia Deng, Lars Maegdefessel, Philip S. Tsao, Atul Butte, Alex A. Morgan

Aging leads to both dilatation and substantial stiffening of the aorta, and constitutes one of the primary risk factors for the development of abdominal aortic aneurysm (AAA), a major source of morbidity and mortality. Using a mouse model of AAA, we propose to study gene expression changes associated with aging and gender, consisting of both mRNA and miRNA profiling of aortic segments. We will develop analysis methods to identify age- and gender-related regulatory gene modules and key miRNA master regulators, which will be tested for disease-modifying therapeutic potential in future studies.

**Nanoscale in situ force measurements to uncover the roles of mechanical force in age-associated ventricular hypertrophy** PI: A. Dunn

Recent observations suggest that molecule-level mechanical forces between cells are critical in governing age-related cardiac tissue remodeling. Current techniques for measuring the forces experienced by cells are ill suited for use with three-dimensional cellular assemblies, and are wholly incompatible with in vivo measurements. We will develop a new fluorescence microscopy technique, termed molecular force microscopy (MFM), that directly visualizes the mechanical forces experienced cells in culture, and eventually in whole organisms. We will use MFM to measure, with millisecond and micrometer accuracy, the fluctuating mechanical forces experienced by cardiomyocytes working against externally applied strain. These measurements will test the working hypothesis that pathological ventricular hypertrophy is the direct result of chronic mechanical stress experienced by cardiomyocytes.

**Telomere Biology & Cardiovascular Aging in Healthy Volunteers** PI: F. Haddad, Co-PIS: S Shen-Orr, C Weyand, M. Davis, Collaborators: Ingela Schnittger, D Liang, J Montoya, A Butte, M.D. Ph.D.

Cardiovascular aging is often associated with progressive atherosclerosis, increased arterial stiffness, impaired ventricular filling and decreased maximal cardiac output with exercise. Studies have shown that several differences in cardiovascular aging exist between men and women and vary according to fitness level. Recent data also suggests that cellular aging reflected by leukocyte telomere length is associated with atherosclerosis and cardiovascular disease risk. Telomere length serves as a marker of replicative immunosenescence. At this time, the relationship between cardiovascular aging and immune aging (also known as immunosenescence) has not been explored in depth. Here, we propose to analyze the relationship between cardiovascular aging, telomere biology and immunosenescence using novel integrative analysis methods. As part of the project, we will also determine cardiovascular aging profiles according to sex and level of activity in a cohort of 300 healthy volunteers.

**Novel metabolic imaging of age-related redox changes and cardiomyopathy in Duchenne's Muscular Dystrophy** PI: H. Blau

Collaborators: F Blankenburg, F Mourkioti, S Sampath, S Sampath, M McConnell

Duchenne muscular dystrophy (DMD), the most common lethal genetic disorder of children, is characterized by continuous injury and progressive degeneration of skeletal and cardiac muscle, and uniformly leads to death from cardiomyopathy and/or diaphragmatic failure. While the molecular mechanism linking dystrophin mutation to cardiac failure remains unclear, altered redox homeostasis has been suggested to play a critical role. In a new cross-departmental collaboration, we have preliminary data describing a novel method for metabolic imaging of the heart, which allows direct readout of the age-related perturbation of redox homeostasis known to occur in DMD. Using a new and clinically relevant mouse model of DMD developed in the Blau lab (Sacco et al 2010, Cell, in press), we have strongly validated this strategy, demonstrating profound cardiac redox abnormalities in aging dystrophic animals, as revealed using non-invasive molecular imaging. Critically, these imaging findings are apparent before symptoms become evident clinically or by echocardiography, providing new insight into and mechanisms for the study of age-related dysfunction in the heart. Seed funding will allow us to develop this imaging reagent in our preclinical model, advance it towards clinical use in DMD patients, and allow us to establish its utility in other forms of cardiomyopathy, including in ischemic disease.



## Events

On Thursday, March 11, 2010, the Stanford Cardiac Electrophysiology Team hosted “Advances in Arrhythmia,” an open house that showcased the new Cardiac Electrophysiology Laboratory and advances in arrhythmia research and care that our electrophysiology team is pioneering. Beginning with a reception in Bing Dining Room, Robert C. Robbins, MD, Cardiovascular Institute director and chair of cardiothoracic surgery, opened the evening by acknowledging the importance of this work in the arrhythmia field. Through its collaborative efforts and major strides to serve the patient population with significant electrical problems of the heart, Cardiac Arrhythmia Service holds a vital place at the Institute.

Led by Paul J. Wang, MD, professor of cardiovascular medicine and director of the Cardiac Arrhythmia Service, the electrophysiology team includes Amin Al-Ahmad, MD, assistant professor of cardiovascular medicine and associate director of the Arrhythmia Service; Henry Hsia, MD, associate professor of cardiovascular medicine and associate director of the Arrhythmia Service; Mintu Turakhia, MD, instructor and cardiac electrophysiologist, and Paul Zei, MD, clinical associate professor of cardiovascular medicine.

The team gave interactive tours of the new Cath Lab area to two groups of 12 couples from the local area with a strong interest in the field. Faculty shared patient stories about the impact of their work and the progress of their research and clinical applications. They answered questions about future directions for non-invasive treatments and the role the electrophysiology team plays in leading the way in transforming treatment of arrhythmia patients. These types of events can help identify and educate potential donors who may have an interest in supporting research efforts in a particular field.

In June, 2010 CVI-sponsored research symposium discussing the biological and environmental causes and medical consequences of sex differences. About 100 people attended the all-day event, titled “Beyond X and Y: The basic and translational science of sex differences,” co-hosted by Women’s Health at Stanford and the Stanford Cardiovascular Institute and held in the Arrillaga Alumni Center.

In September 2010, the CVI held its annual retreat to share research findings and promote cross disciplinary discussions.



View from the northwest

## A New Home for the Cardiovascular Institute

The Stanford School of Medicine is planning the construction of new clinical and research buildings that will reshape medical research on campus. Part of this planning includes a new home for the Cardiovascular Institute. Like the new stem cell building, the Cardiovascular Institute research building will bring cardiovascular researchers and clinicians together to promote interdisciplinary collaborations of the kind that have been shown to be the most fertile ground for scientific breakthroughs. The CVI research building will also bring together basic and clinical scientists in such a way to promote the translation of laboratory science into clinical therapies as rapidly as possible.



Aerial view of the new hospital and research buildings



View from the southeast



## High-Impact Publications of 2010

### Bioengineering

#### **Matrix density mediates polarization and lumen formation of endothelial sprouts in VEGF gradients.**

Shamloo A, Heilshorn SC.  
Lab Chip. 2010 Sep 1.  
PMID: 20820484

#### **The acceleration of implant osseointegration by liposomal Wnt3a.**

Popelut A, Rooker SM, Leucht P, Medio M, Brunski JB, Helms JA.  
Biomaterials. 2010 Sep 21.  
PMID: 20864159

#### **Affibody-based nanoprobes for HER2-expressing cell and tumor imaging.**

Gao J, Chen K, Miao Z, Ren G, Chen X, Gambhir SS, Cheng Z.  
Biomaterials. 2010 Dec 11.  
PMID: 21147502

### Cellular & Molecular

#### **Th17 and Th1 T-cell responses in giant cell arteritis.**

Deng J, Younge BR, Olshen RA, Goronzy JJ, Weyand CM.  
Circulation. 2010 Feb 23;121(7):906-15. Epub 2010 Feb 8.  
PMID: 20142449

#### **Control of macrophage activation and function by PPARs.**

Chawla A.  
Circ Res. 2010 May 28;106(10):1559-69.  
PMID: 20508200

#### **Chromatin remodelling during development.**

Ho L, Crabtree GR.  
Nature. 2010 Jan 28;463(7280):474-84. Review.  
PMID: 20110991

#### **Ligand-specific regulation of the extracellular surface of a G-protein-coupled receptor.**

Bokoch MP, Zou Y, Rasmussen SG, Liu CW, Nygaard R, Rosenbaum DM, Fung JJ, Choi HJ, Thian FS, Kobilka TS, Puglisi JD, Weis WI, Pardo L, Prosser RS, Mueller L, Kobilka BK.  
Nature. 2010 Jan 7;463(7277):108-12.  
PMID: 20054398

#### **A spindle-like apparatus guides bacterial chromosome segregation.**

Ptacin JL, Lee SF, Garner EC, Toro E, Eckart M, Comolli LR, Moerner WE, Shapiro L.  
Nat Cell Biol. 2010 Aug;12(8):791-8. Epub 2010 Jul 25.  
PMID: 20657594

#### **Myosin VI: an innovative motor that challenged the swinging lever arm hypothesis.**

Spudich JA, Sivaramakrishnan S.  
Nat Rev Mol Cell Biol. 2010 Feb;11(2):128-37. Review.  
PMID: 20094053

#### **Chromatin regulation by Brg1 underlies heart muscle development and disease.**

Hang CT, Yang J, Han P, Cheng HL, Shang C, Ashley E, Zhou B, Chang CP.  
Nature. 2010 Jul 1;466(7302):62-7.  
PMID: 20596014

#### **Essential regulation of CNS angiogenesis by the orphan G protein-coupled receptor GPR124.**

Kuhnert F, Mancuso MR, Shamloo A, Wang HT, Choksi V, Florek M, Su H, Fruttiger M, Young WL, Heilshorn SC, Kuo CJ.  
Science. 2010 Nov 12;330(6006):985-9.  
PMID: 21071672

#### **Human melanoma-initiating cells express neural crest nerve growth factor receptor CD271.**

Boiko AD, Razorenova OV, van de Rijn M, Swetter SM, Johnson DL, Ly DP, Butler PD, Yang GP, Joshua B, Kaplan MJ, Longaker MT, Weissman IL.  
Nature. 2010 Jul 1;466(7302):133-7.  
PMID: 20596026

#### **The CRAC channel activator STIM1 binds and inhibits L-type voltage-gated calcium channels.**

Park CY, Shcheglovitov A, Dolmetsch R.  
Science. 2010 Oct 1;330(6000):101-5.  
PMID: 20929812

#### **Contribution of the myosin VI tail domain to processive stepping and intramolecular tension sensing.**

Dunn AR, Chuan P, Bryant Z, Spudich JA.  
Proc Natl Acad Sci U S A. 2010 Apr 27;107(17):7746-50. Epub 2010 Apr 12.  
PMID: 20385849

## **Fgf-9 is required for angiogenesis and osteogenesis in long bone repair.**

Behr B, Leucht P, Longaker MT, Quarto N.  
Proc Natl Acad Sci U S A. 2010 Jun 29;107(26):11853-8. Epub 2010 Jun 14.  
PMID: 20547837

## **In obesity and weight loss, all roads lead to the mighty macrophage.**

Red Eagle A, Chawla A.  
J Clin Invest. 2010 Oct 1;120(10):3437-40. doi: 10.1172/JCI44721. Epub 2010 Sep 27.  
PMID: 20877005

## **Inhibition of vasculogenesis, but not angiogenesis, prevents the recurrence of glioblastoma after irradiation in mice.**

Kioi M, Vogel H, Schultz G, Hoffman RM, Harsh GR, Brown JM.  
J Clin Invest. 2010 Mar;120(3):694-705. doi: 10.1172/JCI40283. Epub 2010 Feb 22.  
PMID: 20179352

## **Impact of Combined Deficiency of Hepatic Lipase and Endothelial Lipase on the Metabolism of Both High-Density Lipoproteins and Apolipoprotein B-Containing Lipoproteins.**

Brown RJ, Lagor WR, Sankaranarayanan S, Yasuda T, Quertermous T, Rothblat GH, Rader DJ.  
Circ Res. 2010 Jun 17.  
PMID: 20558822

## **IL-4/STAT6 immune axis regulates peripheral nutrient metabolism and insulin sensitivity.**

Ricardo-Gonzalez RR, Red Eagle A, Odegaard JI, Jouihan H, Morel CR, Heredia JE, Mukundan L, Wu D, Locksley RM, Chawla A.  
Proc Natl Acad Sci U S A. 2010 Dec 28;107(52):22617-22. Epub 2010 Dec 13.  
PMID: 21149710

## **Population Sciences**

### **Technical feasibility of an online decision support system for acute coronary syndromes.**

DeBusk RF, Miller NH, Raby L.  
Circ Cardiovasc Qual Outcomes. 2010 Nov 1;3(6):694-700. No abstract available.  
PMID: 21081749

### **Maximizing the potential of an aging population.**

King AC, Guralnik JM.  
JAMA. 2010 Nov 3;304(17):1944-5. No abstract available.  
PMID: 21045101

## **INTERMACS Defined Morbidity and Mortality Associated with Pediatric VAD Support at a Single US Center: Stanford Experience.**

Stein ML, Robbins R, Sabati AA, Reinhartz O, Chin C, Liu E, Bernstein D, Roth S, Wright G, Reitz B, Rosenthal D.  
Circ Heart Fail. 2010 Aug 31.  
PMID: 20027182

## **Interagency Registry for Mechanically Assisted Circulatory Support (INTERMACS)-defined morbidity and mortality associated with pediatric ventricular assist device support at a single US center: the Stanford experience.**

Stein ML, Robbins R, Sabati AA, Reinhartz O, Chin C, Liu E, Bernstein D, Roth S, Wright G, Reitz B, Rosenthal D.  
Circ Heart Fail. 2010 Nov 1;3(6):682-8. Epub 2010 Aug 31.  
PMID: 20807863

## **Defining the Limits of Athlete's Heart. Implications for Screening in Diverse Populations.**

Sedehi D, Ashley EA.  
Circulation. 2010 Feb 22. No abstract available.  
PMID: 20176992

## **Measurement Precision in the Optimization of Cardiac Resynchronization Therapy.**

Turcott RG, Witteles RM, Wang PJ, Vagelos RH, Fowler MB, Ashley EA.  
Circ Heart Fail. 2010 Feb 22.  
PMID: 20176716

## **Anatomic and functional evaluation of bifurcation lesions undergoing percutaneous coronary intervention.**

Koo BK, Waseda K, Kang HJ, Kim HS, Nam CW, Hur SH, Kim JS, Choi D, Jang Y, Hahn JY, Gwon HC, Yoon MH, Tahk SJ, Chung WY, Cho YS, Choi DJ, Hasegawa T, Kataoka T, Oh SJ, Honda Y, Fitzgerald PJ, Fearon WF.  
Circ Cardiovasc Interv. 2010 Apr;3(2):113-9.  
PMID: 20407111

## **Genomics, Proteomics, & Bioinformatics**

### **Pharmacogenomics: will the promise be fulfilled?**

Altman RB, Kroemer HK, McCarty CA, Ratain MJ, Roden D.  
Nat Rev Genet. 2011 Jan;12(1):69-73. Epub 2010 Nov 30.  
PMID: 21116304

### **Cell type-specific gene expression differences in complex tissues.**

Shen-Orr SS, Tibshirani R, Khatri P, Bodian DL, Staedtler F, Perry NM, Hastie T, Sarwal MM, Davis MM, Butte AJ.  
Nat Methods. 2010 Apr;7(4):287-9. Epub 2010 Mar 7.  
PMID: 20208531



## **Inaugural Article: Completely phased genome sequencing through chromosome sorting.**

Yang H, Chen X, Wong WH.

Proc Natl Acad Sci U S A. 2011 Jan 4;108(1):12-7. Epub 2010 Dec 15.

PMID: 21169219

## **MiDReG: a method of mining developmentally regulated genes using Boolean implications.**

Sahoo D, Seita J, Bhattacharya D, Inlay MA, Weissman IL, Plevritis SK, Dill DL.

Proc Natl Acad Sci U S A. 2010 Mar 30;107(13):5732-7. Epub 2010 Mar 15.

PMID: 20231483

## **High throughput sequencing reveals a complex pattern of dynamic interrelationships among human T cell subsets.**

Wang C, Sanders CM, Yang Q, Schroeder HW Jr, Wang E, Babrzadeh F, Gharizadeh B, Myers RM, Hudson JR Jr, Davis RW, Han J.

Proc Natl Acad Sci U S A. 2010 Jan 26;107(4):1518-23. Epub 2010 Jan 4.

PMID: 20080641

## **Imaging**

### **A molecularly engineered split reporter for imaging protein-protein interactions with positron emission tomography.**

Massoud TF, Paulmurugan R, Gambhir SS.

Nat Med. 2010 Jul 18.

PMID: 20639890

### **Colloidal lenses allow high-temperature single-molecule imaging and improve fluorophore photostability.**

Schwartz JJ, Stavakis S, Quake SR.

Nat Nanotechnol. 2010 Feb;5(2):127-32. Epub 2009 Dec 20.

PMID: 20023643

### **Noninvasive molecular imaging of c-Myc activation in living mice.**

Fan-Minogue H, Cao Z, Paulmurugan R, Chan CT, Massoud TF, Felsher DW, Gambhir SS.

Proc Natl Acad Sci U S A. 2010 Aug 16.

PMID: 20713710

### **Timing of bone marrow cell delivery has minimal effects on cell viability and cardiac recovery after myocardial infarction.**

Swijnenburg RJ, Govaert JA, van der Bogt KE, Pearl JJ, Huang M, Stein W, Hoyt G, Vogel H, Contag CH, Robbins RC, Wu JC.

Circ Cardiovasc Imaging 2010 Jan;3(1):77-85 Epub 2009 Nov 17.

PMID: 19920031

## **Human ferritin cages for imaging vascular macrophages.**

Terashima M, Uchida M, Kosuge H, Tsao PS, Young MJ, Conolly SM, Douglas T, McConnell MV.

Biomaterials. 2011 Feb;32(5):1430-7. Epub 2010 Nov 11.

PMID: 21074263

## **Three-dimensional tracking of single mRNA particles in Saccharomyces cerevisiae using a double-helix point spread function.**

Thompson MA, Casolari JM, Badieirostami M, Brown PO, Moerner WE.

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